Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Combined Dystonia With Self-Mutilation in 6-Pyruvoyl-Tetrahydropterin Synthase (PTPS) Deficiency: A Case Report

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Monoamine-related neurotransmitter diseases refer to several neurological syndromes caused by primary and secondary defects in the biosynthesis, degradation, or transport of catecholamines and serotonin. Tetrahydrobiopterin (BH4) deficiency exemplifies such a disease. BH4 is an essential cofactor for levodopa, serotonin, and tyrosine syntheses. 6-Pyruvoyl-tetrahydropterin synthase (PTPS) is involved in BH4 biosynthesis and its deficiency is the most common BH4 disorder, causing an autosomal-recessive condition clinically characterized by neurodevelopmental delay, truncal hypotonia, extrapyramidal features, and swallowing difficulties.[1,2] Behavioral problems, such as irritability, obsessive-compulsive disorder, and aggressiveness, are also common.[1,3,4] PTPS deficiency can be prevented by presymptomatic diagnosis, by means of neonatal screening test for hyperphenylalaninemia, and treatment.

Here, we present a case of PTPS deficiency with combined dystonia and marked behavioral problems and self-mutilation, a feature typically observed in other conditions, such as Lesch-Nyhan syndrome (LNS) and chorea-acanthocytosis (ChAc).[5,6]

Case Report

A 21-year-old Iranian man, born to consanguineous parents, was floppy during his first year of life, unable to hold his head and sit without support. In early infancy, based on his high levels of serum phenylalanine, a diagnosis of phenylketonuria was raised. However, no investigation into the biopterin pathway was undertaken at this time.

At the age of 6, he developed severe neurodevelopmental delay with learning difficulties and swallowing problems. He was finally diagnosed with PTPS deficiency after appropriate neurometabolic investigation (based on his total biopterins and dihydropteridine reductase enzyme levels). L-dopa, 5-hydroxytryptophan, and BH4 treatment was started, which improved his motor skills and swallowing ability. In the following years, he improved clinically, but a severe behavioral disorder began to appear.

At 19, he could walk aided and understand simple commands. However, his speech and language were poorly developed with repetitive vocalizations and guttural sounds. He had microcephaly and a dysmorphic face, pseudobulbar affect with easy laughing, and a pronounced behavioral disorder resembling oppositional defiant behavior in the context of a severe intellectual disability. The behavioral disorder included overaggressiveness and self-mutilation as well as biting his lips, hands, and fingers. He also banged his head and arms against the wall, particularly when tired or upset. He displayed oromandibular and limb dystonia, stereotypies, and choreic movements. At that time, his treatment consisted of L-dopa 100/25 mg QDS, 5-hidroxytryptophan 100 mg QDS, and sapropterin 150mg OD.

His motor and cognitive symptoms are currently stable; however, managing his aggressiveness and self-mutilation continues to be a challenge (Video S1).

Discussion

This is the first report of PTPS deficiency presenting with dystonia and severe behavioral disturbance, particularly self-mutilation.

Dystonia and self-mutilation have a brief list of differential diagnoses, including LNS and ChAc.[5,6] The most common self-injurious behavior in LNS and ChAC is self-biting (finger, lips, and cheek), although head scratching may also be present in ChAC.[6] Our patient tends to injure himself by lips and finger biting, in addition to beating his head and arms.

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Keywords: PTPS deficiency, self-mutilation, neurotransmitters, serotonin, dopamine.
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Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 25 July 2018; revised 19 September 2018; accepted 25 September 2018.
Published online 8 November 2018 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.12698

There are several hypotheses to explain the pathophysiology underlying self-mutilation in LNS, such as increased plasma met-enkephalin and serum b-endorphin levels, peripheral neuropathy, decreased striatal dopamine (DA) levels, and increased serotonin activity.[7] For instance, in LNS the low levels of presynaptic DA in the basal ganglia and upregulation of dopamine D2 receptors in the striatum lead to neurochemical phenomena called "receptor supersensitivity."[7] Impairments in the DA pathway may additionally increase the turnover of serotonin, which seems to facilitate DA-mediated behavioral supersensitivity. Moreover, DA and serotonin may cause striatal cells to switch from an inhibitory to excitatory state.[7] These neurotransmitter changes, together with the above-proposed mechanisms, are thought to be implicated in the pathophysiology of self-injurious behavior in LNS.[7] Pharmacological trials support this hypothesis.[7] Additionally, there are reports of improvement in dystonia and self-mutilation with bilateral stimulation of the globus pallidus internus (GPi) in LNS, which indicates that self-injurious behavior may be related to basal ganglia dysfunction.[8]

ChAc is caused by VPS13A gene mutations on chromosome 9, which normally codes for chorein, located in the dense-core vesicles where DA is also stored. Chorein is decreased in ChAc and involved in potassium-induced DA release, affecting striatal dopamine levels.[9] Self-mutilation in ChAc is reported to improve with quetiapine, an atypical antipsychotic with a high affinity to 5-hydroxytryptamine 2a (5HT2a) receptors and low affinity for D2 receptors, but not with typical antipsychotics with antagonistic activity for DA D2 receptors.[10] This further suggests that serotonergic and dopaminergic pathways are affected in ChAc and are possibly involved in the pathophysiology of self-mutilation.

PTPS deficiency is a BH4 disorder, which results in depletion of serotonin and DA in the brain.[3] Using the same analogy of LNS and ChAC, we may argue that the dysfunctional dopaminergic and serotonergic systems might be the cause of the self-injurious behavior observed in this condition.

Self-mutilation therapy includes different approaches, such as behavioral therapy, several drugs, and DBS.[8,11] It is difficult to say which one might be the most effective in this case, but in view of its efficacy in other disorders for both dystonia and self-mutilation, GPi-DBS might be an option to consider.

In conclusion, this case illustrates that PTPS deficiency, which affects dopaminergic and serotonergic pathways, should be included in the differential diagnoses of dystonia and self-mutilation to promote early diagnosis and possible treatment.

Authors' Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript: A. Writing of the First Draft, B. Review and Critique.

A.L.: 1A, 1B, 1C, 2A

P.S.: 1A, 1C

M.S.: 1A, 1C

A.J.: 2B

K.P.B.: 1A, 2B

Disclosures

Ethical Compliance Statement: We hereby confirm that the present study conforms to the ethical standards and guidelines of the Journal. The patient has given written and informed consent for online publication of her videos.

Funding Sources and Conflicts of Interest: The authors report no sources of funding and no conflicts of interest.

Financial Disclosures for previous 12 months: The authors declare that there are no disclosures to report.

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Supporting Information

Supporting information may be found in the online version of this article.

Video S1. The patient at the age of 19. Findings are consistent with self-mutilation and overaggressiveness, including lip and finger biting, squeezing own neck, scratches and bruises on arms indicative of arm beating, and aggressive nature toward others. Microcephaly, choreodystonic oromandibular movements, and poor language development are also evident.